

# Clinical Trial(s) Design for products intended for very small population: FDA perspective

Nisha Jain, M.D.

FDA/CBER/OBRR/DH



# Overview

- Definition
- Introduction
- Products licensed in US for very small patient population
- Trial design recommendations
  - plasma derived product
  - Recombinant or other novel product
- Procedures for approval
- Post marketing data collection



# Definition

Section 526 (a) (2) of the FDC Act defines “rare disease or condition” for purposes of Orphan drugs:

- A) Any disease or condition which affects less than 200,000 persons in US, or
- B) Affects more than 200, 000 in US and for which there is no reasonable expectation that cost of developing and making available in US for such disease or condition will be recovered from sales in the US of such drug.



# Scope of the Workshop

- Limited to
  - Only plasma protein disorders that affects very small population: tens or few hundreds
    - Congenital Factor XIII deficiency
      - Prevalence: 1 in 1,000,000
      - Pattern of inheritance: Autosomal recessive
      - 200 patients have been described worldwide
      - Homozygotes present with life long bleeding
      - Prophylaxis required every 3-4 weeks because of prolonged half life



# Scope

- Congenital ATIII
  - Prevalence 1in 2000-5000
  - Pattern of inheritance: autosomal dominant
  - Otherwise Normal: do not require At replacement therapy.
  - At risk of thromboembolism only during surgery and pregnancy
    - » Risk is high as 50- 60%
- “Super rare diseases or conditions”



# FDA Challenges

- Quantity of Evidence necessary to support effectiveness and safety
  - limited by small sample size
  - estimates of safety and efficacy may have wide variability
  - “Adequate and well controlled” often difficult
    - appropriateness of Historical controls
    - Natural history
- Use of surrogate endpoints leads to reliance on Post Marketing data collection (PMC)
  - Limitations
- No provision for temporary license like in Europe
- Real need of the product is not established
  - Use of FFP for many of the conditions



# Industry Issues

- Costly for development
  - Limited market
  - Not profitable
- Not much incentives
  - Except for the larger off label market where the product has not been studied
- ? Regulatory challenges



# Product(s) currently licensed in US: Plasma derived

Thrombate III (Bayer): Antithrombin III (Human)  
Plasma derived: Licensed in 1991

- Indication: for treatment of patients with hereditary ATIII deficiency in connection with
  - a) surgical or obstetrical procedures
  - b) or when they suffer from thrombo-embolism
- Studies for licensure:
  - Preclinical:
    - » *In vitro* Characterization: Physico chemical properties and biological activity
    - » Animal: Both acute and repeat dose toxicologic study



# Product(s) currently licensed in US : Plasma derived

- Clinical studies:
  - PK study :
  - 10 asymptomatic patients infused with single dose of 100 IU/kg ATIII
    - Mean *in vivo* recovery
      - » immunologic assay 1.6% per unit per Kg administered
      - » Functional assay 1.4% per unit pre kg administered
    - Half life
      - » Immunologic assay: 2.5 days
      - » Functional assay: 3.8 days

# Product(s) currently licensed in US : Plasma derived

- Evaluate efficacy: open label, single arm
  - 13 patients with previous history of thromboembolism including Pulmonary embolism
  - 11 surgery and 5 delivery
  - Heparin in 3 of the 11 surgical and 5/5 deliveries
  - Dose was calculated to maintain plasma levels at 70-120%
  - Duration of treatment ranged from 8-23 days.
  - Outcome:
    - No patient developed thrombosis
    - Substantial evidence of effectiveness

# Product(s) currently licensed in US : Plasma derived

- Safety:
  - Infusional toxicities
  - Viral transmission
    - No viral transmission over 13 month follow up period

# Products licensed in US

- Humate P: Antihemophilic factor/von Willebrand factor complex factor
  - Originally licensed ( 1986) for treatment and prevention of spontaneous and traumatic bleeding in Hemophilia A
  - In 1999 licensed for severe von Willebrand disease or mild and moderate where desmopressin is not adequate



# Products licensed in US

- Licensure of new indication based on following studies:
  - Interim report of prospective PK study in asymptomatic patients with vWD ( types 1, 2 and 3)
  - Efficacy and safety: retrospective review of data from 97 Canadian vWD patients who were given the product under Canadian emergency drug release program
    - Efficacy rating as excellent in 100% in Type1, 2A and B and 95% in Type 3 patients
    - Adequate dosing information could be gathered from the retrospective review
    - Post Marketing Commitment: To evaluate the product for elective surgical use in vWD patients



# Products licensed in US

Recombinant:

None licensed for the very very small patient population



# Clinical trial design (1)

## Introduction:

- Case by case basis
  - Different products require different development program
  - Different disease need different types of evaluation
  - No statutory provision for generic biologicals



# Clinical trials: (2)

## Plasma derived:

New product:

- Preclinical
  - Well characterized *in vitro*
    - » Physico chemical properties and biological activity
  - Animal studies:
    - » Limited/ relevant toxicologic studies
    - » ?Relevant model available: dose ranging and efficacy study



# Clinical trials (3)

- Clinical
  - PK/PD study:
    - asymptomatic condition
    - Standard PK parameters
    - Sample size: variable, usually 12-15 patient
  - Dose ranging study
  - Efficacy and safety study in appropriate patient population
    - Efficacy:
      - » clinical endpoints
      - » Surrogate markers
      - » Controlled study: ? Historical control



# Clinical trial(3)

- Safety:
  - Limited pre-licensure
  - Immunogenicity data is usually not adequate pre-licensure
  - Post Licensure
- Statistical consideration:
  - More efficient design
  - One sided
  - Reduced power
- Post marketing evaluation
  - Both efficacy and safety



# Clinical trials (4)

- A licensed product for the same indication already available
  - Comparative cross over PK with the licensed product
  - Some efficacy and safety data pre-licensure
  - Post marketing efficacy and safety data



# Clinical trials (5)

- Foreign data (product licensed in other countries)
  - Is acceptable if it meets the requirement of 21 CFR 312.120:
    - “FDA accepts such studies provided they are well designed, well conducted, performed by qualified investigators and conducted in accordance with ethical principles acceptable to the world community. Studies meeting these criteria may be utilized to support clinical investigations in the United states and/or marketing approval. Marketing approval of a new drug based solely on foreign clinical data is governed by 314.106”



# Clinical trials (6)

- 21 CFR 314.106: As sole basis for marketing approval.
  - “An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if : (1) the foreign data are applicable to the U.S. population and U.S. medical practice (2) the studies have been performed by clinical investigators of recognized competence and (3) the data may be considered valid without the need for an on site inspection by FDA or if FDA considers such an inspection to be necessary.”



# Clinical trials (7)

- Recombinant/ Novel entity:
  - Preclinical:
    - *In vitro* characterization;
      - Physico chemical properties, biological activity
    - Animal studies
      - Toxicology studies: single dose, repeat dose
      - Efficacy /dose ranging in appropriate models



# Clinical trials: Recombinant products (8)

- PK/safety
  - Comparative PK with the plasma derived product
    - If PK comparable to Plasma derived product: same dosing schedule may be applicable
    - If PK not comparable:
      - » Dose ranging study to establish the appropriate dose to maintain appropriate plasma levels
      - » comparable assay to detect biological activity



# Clinical trials (9)

- Efficacy:
  - Clinical endpoints/ surrogate marker
  - ? Control ( historical)/ active control with the plasma derived product
  - Statistical consideration:
    - » More efficient design to show evidence of effectiveness
    - » ?One sided confidence interval
    - » ?reduced power
  - Safety
    - » Immunogenicity: well developed assays to detect neutralizing antibodies
    - » General safety
- Post Marketing Commitment
  - Efficacy and safety



# Clinical trials (10)

- Product is licensed for one indication but can be used for another indication
  - PK in the relevant population for the relevant indication
  - Efficacy in the relevant population
  - Safety in the relevant population if reason to believe that safety is different.
  - PMC



# FDA Incentives

- Orphan drug status/ grant
- Faster methods of approval
  - Accelerated approval:
    - Surrogate endpoint
    - [www.fda.gov/cber/gdlns/](http://www.fda.gov/cber/gdlns/)
  - Priority review
    - 6 month review
    - [www.fda.gov/cber/gdlns/](http://www.fda.gov/cber/gdlns/)

